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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/418,221	10/14/99	MAHANTHAPPA	N ONV-043.01(1

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EXAMINER	
MESSENDORF, T	
ART UNIT	PAPER NUMBER
1627	//

DATE MAILED:
08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/418,221	Mahanthappa
Examiner Teresa Wiesenhofer Grace Hour	Art Unit 1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 23, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. A Petition for a Three Month Extension of Time, A Response Under 37 C.F.R. 1.111, A Change of Address and A Change of Attorney Docket Number, respectively received May 23, 2001 were entered respectively as Paper Nos. 7-10.

Status of the Claims

2. Claims 1-37 are pending in the instant application.

Response to the May 23, 2001 Response and Amendment Under 37 C.F.R. 1.111

3. Applicants' arguments filed in the May 23, 2001 July 18, 2000 Amendment have been fully considered and discussed below, under each corresponding section heading.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objection(s) and/or Rejection(s)

5. The objection to the specification, because:

[a] use of a hyperlink at page 1, line 26
[b] typographical errors e.g., "rates"(should be rats) at page 11, line 3

is withdrawn in light of applicant's amendments.

6. The rejection of claims 1-37 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in light of applicant's amendments.

7. The following rejections of claims 1-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of applicant's amendments:

[A] claim 1 is unclear as to the ischemic or epoxic conditions i.e., the metes and bounds of the recited conditions are not clearly set forth and the conditions that would be required for ischemic or epoxic.; a ptc therapeutic is unclear and goes against the conventional use of a compound. Furthermore, the use of abbreviations such as PKC or ptc or KT 5720 is indefinite. It is suggested that applicants provide for the complete names.

[B] claims 2-6 for being indefinite in reciting the term "therapeutic" twice;

[C] claim 3 is a duplicate of claim 2 since the same method steps is recited and it is considered that treatment of cerebral infractions is a protection of cerebral tissues as recited in claim 2.

[E] The term "small" within the claimed context is indefinite. Said term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

[F] claims 11-13 determination of the different transduction signals is indefinite as applied to administration in an individual.

[G] Regarding claim 16, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Also, the phrase "can independently" and "stability permit" fail to ascertain the claimed invention with precision. It is suggested that applicants recite for the number of carbon units present in the alkylene group in lieu of the relative term "lower". Furthermore, it is not clear as to the substituents present in the N-form of R1 and R2 e.g., the metes and bounds of said substituents are not clearly set forth.

[H] "The patient" in claim 22 lacks antecedent basis of support.

[I] Claim 24 recitation of "the mammal" lacks antecedent support from the base claim and broadens the base recitation of an "individual".

8. The rejection of claims 1-16 and 18-37 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Maiese et al (5,519,035) or Satoh et al (British Journal of Pharmacology) are withdrawn in light of applicant's amendments.

9. The rejection of claims 1-16 and 18-37 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Andrulis et al (5,643,915) are withdrawn in light of applicant's amendments

10. The rejection of claim 17 under 35 U.S.C. 103(a) as obvious over anyone of any one of Maiese or Satoh or Andrulis in view of Ikegaki et al (5,747,507) are withdrawn in light of applicant's amendments.

Outstanding Objection(s) and/or Rejection(s)

11. The rejection of claims 1-37 under 35 U.S.C. 101 due to the claimed invention lacks patentable utility **is maintained for the following reasons of record.**

The claimed invention drawn to a method of protecting cerebral tissue, treating cerebral infarctions and damage to neuronal cells or a stroke lacks patentable utility. To date there is no specific therapy for cerebral thrombosis or embolism.

The specification is merely replete with general statements and a showing limited to a focal stoke model that involves the middle cerebral artery occlusion in rats. The tests merely measures the volume of cerebral infarction. There is no indication that such models would be predictive of similar effect to the intended host and more importantly whether the single

compound, Shh tested therein is applicable to the infinite ptc therapeutic as claimed or to a more severe form of stroke especially those affecting the supply of oxygen to the brain.

In the May 23, 2001 Amendment, applicant asserts that:

[1] the above-identified rejection is traversed, because:

a prima facie lack of utility has not been established in the November 21, 2000 Office Action, because the Examiner has provided no evidence suggesting that the animal models use are inadequate to test effectiveness for stroke therapies; and

that the example of Shh is sufficient to indicate that the broader class of ptc therapeutics would be effective in the claimed methods.

In response, it is the position of the Examiner that:

[1] applicants' arguments and declaration have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record.

without any further reiteration, note that the arguments set forth in the April 6, 2000 Office Action of record are still applicable.

However, the following points are set forth below:

with regard arguments regarding the establishment of a prima facie lack of utility, applicant's:

is directed to Ex parte Balzarini, supra at 1897 where the Board of Patent Appeals and Interferences provided guidance, "We do not presume to tell Applicants what evidence would be acceptable in rebuttal of these rejections. While we are no requiring human clinical trials, it may very well be that in 1987 or even now those skilled in this art would not accept anything short of such human clinical trials. There is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy." Absent evidence directed to the claimed treatment methods, the instant claims are properly rejected under 35 USC 101; and

Applicants assert that documentary evidence should have been used by the Examiner to support the assertion that the claimed libraries lack utility under 35 USC 101. Applicants' assertion is misplaced. Documentary evidence is recommended whenever the Office asserts that a stated, specific utility would not be credible in the mind of one of ordinary skill in the art. Here, no specific utility is asserted, therefore, there is no presumption to rebut.; and

the example of Shh or sonic hedgehog gene is insufficient to indicate that the broader class of ptc therapeutics would be effective in the claimed methods, because it is merely a representative example of a type of hedgehog gene.

In light of the foregoing, the rejection is maintained for reasons of record and is deemed proper.

12. The following rejections of claims 1, 7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **are maintained for the following reasons of record (for applicant's convenience each rejection, applicant and Examiner response is discussed separately below**:

[A] claim 1, the phrase "cerebral infarct volume" is unclear and inconsistent with the preamble recitation of neuronal cells. Also, it is not clear as to the recitation of the function of the ptc therapeutic in the recited method.

In the May 23, 2001 Amendment, applicant's assert that with regard to:

the term "cerebral infarct volume" is not indefinite, because:

the relationship between ischemia and infarct it is used/explained throughout the specification;

is a term conventionally understood by the ordinary artisan; and

and is defined in the in the instant "specification at page 2, lines 6-19, which explains how ischemia and infarctions are related.

In response, it is the position of the Examiner that:

applicants' arguments and declaration have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record.

the term "cerebral infarct volume" within the context of claim 1 remains vague and indefinite as it is unclear what the aforementioned phrase refers to when read within the context of the specification and claim 1, i.e.,

the instant specification recites only that ischemia results from an inadequate supply of blood to the brain tissue, while "an infarct is an area of cell death or necrosis" at page 2, lines 16-19,

In light of foregoing, the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize

what material constitutes cerebral infarct volume (i.e., is volume attributable to dead or necrosed brain cell mass?") or

when the phrase "cerebral infarct volume" is read within the context of claim 1, against what standard measure is the absence of administration of the ptc therapeutic determined in order to measure or determine what quantities of the claimed therapeutic regimen should be administered in order to reduce whatever material might constitute said undefined "cerebral infarct volume"?

In light of the foregoing, clarification still is requested from applicant, i.e., it may be helpful to point to where support is found in the instant specification.

[D] claim 7 is indefinite as to the binding effect of the ptc therapeutic as determined when administered to an individual and unclear as to how it mimics hedgehog-mediated patched signal transduction, within the claimed context.

In the May 23, 2001 Amendment, applicant's assert that with regard to:

[D] how a "ptc therapeutic would mimic hedgehog-mediated patched signal transduction " is not unclear, because:

the instant "specification at page 5, lines 12-18, give examples of how a ptc therapeutic **might mimic** hedgehog-mediated patched signal transduction"; and

one of skill in the art would understand the concept of hedgehog mediated patched signal transduction and would not find the aforementioned term indefinite.

In response, it is the position of the Examiner that:

applicants' arguments and declaration have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record.

how a "ptc therapeutic would mimic hedgehog-mediated patched signal transduction " is unclear and indefinite, because:

the instant specification recites only that "the therapeutic can be , e.g., a molecule which binds to patched and mimics hedgehog-mediated patched signal transduction. For instance, the binding of the therapeutic to patched **may result** in upregulation of patched and/or gli expression" at page 5, lines 12-18,

In light of foregoing, the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize

how a "ptc therapeutic" mimics a "hedgehog-mediated patched signal transduction " without the identification of some ptc therapeutic structure or chemical core structure, because:

It is conventionally known in the art that structure activity relationships (consideration of property based parameters, such as hydrophobic, electronic and or steric functional group character and interactions; i.e., e.g., such as position of the individual functional groups in a molecule) may critically affect, indicate or show biological activity, such as mimicking a particular biological function.

Molecular conformation, i.e. the shape size plus conformation that a molecule prefers is of great importance on determining whether the interaction of that molecule with a receptor will bring the appropriate atoms near each other.

For example, in certain cases even a small functional group change can render a molecule inactive for its particular substrate, biological activity etc.

Moreover, the ordinary artisan understands that it is not always easy to measure SAR parameters, particularly ones related to steric effects, where one rarely knows which properties are likely to be relevant.

(see generally, Foye et al., Chapter 3-5: "Biopharmaceutical Properties of Drug Substances", "Structural Features and Pharmacologic Activity", and "Theoretic Aspects of Drug Design", Principles of Medicinal Chemistry, Baltimore: Williams & Wilkins, Copyright 1995, pages 12-57).

In particular, applicants have not taught by what means or how a "ptc therapeutic" hedgehog signal transduction and the examples cited by applicants are not sufficient to show that a"ptc therapeutic" mimics or affectuates a biological activity.

In light of the foregoing, clarification still is requested from applicant, i.e., it may be helpful to point to where support is found in the instant specification.

In the May 23, 2001 Amendment, applicant's assert that:

> the determination of the different transduction signals is indefinite as applied to administration in an individual in claims 11-13 is not unclear, because:.
>
> the manner in which a ptc therapeutic interacts with or affects a protein in the hedgehog pathway can be determined using standard biochemical techniques;
>
> "Because most human individuals exhibit an extremely high degree of homology between their proteins, the ordinary artisan "would expect that the mode of action elucidated in vitro would be consistent with its mode of action in vivo"; and
>
> "thus, determining whether a particular method falls within the scope of the claim would not require investigating the molecular actions within a particular patient".

In response, it is the position of the Examiner that:

> applicants' arguments and declaration have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record.

In light of the foregoing, each of the above-identified rejections are maintained for reasons of record and is deemed proper.

New Grounds of Rejection

13. The following new grounds of rejection are necessitated by applicants' amendments.

Specification

14. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: As the claims of the instant application have been amended to recite the term "hypoxic", instead of the term "epoxic", applicants are requested to review the specification

and to amend the specification to recite in stances where the term "hypoxic" appears to recite the term "epoxic." For example, the term "epoxic conditions" is recited at page 4, line 11 and page 12, line 22 of the instant specification, which should be amended to recite "hypoxic conditions" accordingly.

New Matter

15. Claims 1-37 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The added material of the amended claims 1-37, which are not supported by the original disclosure is as follows: the specification **does not teach** the recitation of the terms as indicated below in ***bold and by underlining***:

the terms as recited in claims 1-6, from which claims 7-37 depend:

[1] "a **therapeutic regimen** including administering a hedgehog polypeptide **and** administering a ptc therapeutic";

Also note that the instant specification only refers to "pre- or post surgical administration of the hedgehog and/or ptc therapeutics of the present invention will treat or prevent the resulting ischemia" as directed only to the issue of "treating the adverse neurological consequences of surgery" (see specification at page 16, lines 28-29 to page 17, lines 1-6, especially lines 3-4)

[2] "the **absence of administration** of the ptc therapeutic **and** the hedgehog polypeptide"

[3] "ptc therapeutic is a . . . **a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase or an antagonist of cAMP**"

Note that the instant specification **only refers** to the fact that "the **hedgehog pathway** can be agonized by antagonizing the cAMP pathway, e.g., by using an agonist of a cAMP phosphodiesterase or by using an antagonist of adenylate cyclase, cAMP or protein kinase A (see, instant specification at page 59, lines 8-11)", but does not state that a ptc therapeutic is as selected from the aforementioned agonists, antagonists, etc.; and

In claim 34:

[5] "a hedgehog polypeptide **and** a small molecule antagonist pf patched."

Accordingly, there is lack of descriptive support for the above-identified terms, wherein the components, substituents, elements, etc. of the claimed invention are other than those recited supra. **In accordance with M.P.E.P. Section 714.02, applicants should specifically point out support for any amendments made to the instant disclosure.**

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 U.S.C. § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claims 13, 34 are vague and indefinite in that the following terms are not defined in the preamble of those claims: [1] "a small organic molecule . . . which binds to patched (as in claim 13)", "a small molecule antagonist of patched (as in claim 34)"; it is unclear what the term "patched" refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what or how the generic term "patched" means relative to the generic term "small molecule" or "a small molecule antagonist" defines (i.e., a small molecule which binds to patched what?, a small molecule of patched what?"- what is the noun object or object of a prepositional phrase to which the term "patched" refers?); applicant is requested to point to where in the specification that those terms are defined and to explain what the aforementioned phrase means. Clarification is requested.

19. Claims 1-6 are vague and indefinite, because of improper Markush group language as related to the definition of "ptc therapeutic is a . . . a cAMP phosphodiesterase agonist, an antagonist of adenylate cyclase ot an antagonist of cAMP." The identified claims should be amended to recite the proper Markush format, set forth as either "wherein R is selected from the group consisting of A, B, C and D" or alternatively "wherein R is A, B, C or D." (see, Ex parte Markush, 1925 C.D. 126, Comm'r. Pat. 1925 and M.P.E.P. 2173.05(h)). Appropriate correction is requested.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to T. Wessendorf whose telephone number is (703) 308-3967. The Examiner can normally be reached Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Jyothsna Venkat Ph.D., can be reached on (703) 308-0570. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Venkat

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

T. Wessendorf

August 12, 2001